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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,178	07/02/2007	Masaaki Oka	3462.1015-000	6214
21005 7590 11/02/2009 HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133 CONCORD, MA 01742-9133			EXAMINER AEDER, SEAN E	
			ART UNIT 1642	PAPER NUMBER
			MAIL DATE 11/02/2009	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/552,178	Applicant(s) OKA ET AL.	
	Examiner SEAN E. AEDER	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 July 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 13 and 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/2/07; 5/27/08; 11/24/08; 8/19/09</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Election/Restriction

The Election filed 7/27/09 in response to the Office Action of 5/1/09 is acknowledged and has been entered. Applicant elected group I. Applicant did not elect a species and traversed a requirement to elect a species.

The traversal is on the ground(s) that the claims do not presently recite specific genes or combinations of genes. This is found persuasive. However, Applicant is forewarned that a species election will be required if claims are amended to recite particular genes or combinations thereof. Upon withdrawing the election of species requirement, the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-15 are pending.

Claims 13-14 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-12 are currently under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-12 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Applicant is invited to review the OG notice of 11/22/05 (<http://www.uspto.gov/web/offices/com/sol/og/2005/week47/patgupa.htm>). When a method claim does not result in a physical transformation of matter, the claim may be statutory when it recites a **concrete, tangible**, and useful result. In the instant case, the claims are directed to methods of defining the differentiation grade of a tumor based on expression levels or patterns of genes. The claims lack any recited method of physical transformation of matter. Further, although the recited method may be useful, the method does not recite a concrete or tangible result. It appears that the result is an expression level(s); however, the expression level(s) is not concrete because the claims do not distinctly point-out *exactly* what each expression level(s) *means*. Further, the result is not tangible because the claims do not recite a means of communicating the result to a user. This rejection could be obviated by incorporating a method of physical transformation, such as an active method of performing an assay, in independent claim(s) 1 and 10-12. Alternatively, this rejection could be obviated by amending independent claim(s) 1 and 10-12 to recite a method with a concrete, tangible, and useful result. Note that this is not a utility rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "the statistical analyses". There is insufficient antecedent basis for "the statistical analyses" in the claim.

Claim 6 recites "the Fisher ratio". There is insufficient antecedent basis for "the Fisher ratio" in the claim.

Claims 7-9 recite "the number of the genes and/or proteins". There is insufficient antecedent basis for "the number of the genes and/or proteins" in the claims.

Claims 11-12 recite "selecting a number of genes and/or proteins decided in step (a)". Step "(a)" of claims 11-12 recite methods of "determining" and not methods of "deciding". Therefore, it is unclear which genes and/or proteins are "decided" in step (a) of claims 11-12.

Claims 11-12 recite "applying the data of genes and/or proteins selected in step (b)". It is unclear what are the "data" of genes and/or proteins selected in step (b) of claims 11-12.

Claims 11-12 recite method of “applying” various things to “all samples”.

Because claims 11-12 do not recite any samples, it is unclear as to what samples things are to be applied.

35 USC § 102 / 35 USC § 103

It is noted that the rejections under 35 U.S.C. 102 and 35 U.S.C. 103 set-forth below are meant to expedite prosecution of this application and address what the Examiner suspects Applicant is attempting to claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Okabe et al (Cancer Research, March 2001, 61: 2129-2137).

Okabe et al teaches a method of defining the differentiation grade of a tumor with genes selected by statistical analysis using microarrays based on expression level or pattern of genes of human liver tumor tissues, wherein the differentiation grade of tumor is selected from the group consisting of non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC and wherein the genes are differentially expressed between non-cancerous liver and pre-

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cancerous liver, precancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC (see pages 2136-2137, in particular). Okabe et al further teaches the importance of analyzing microarray data of tumor states using cluster analysis (see page 2137, in particular).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) as applied to claims 1-5 above, and further in view of Adorjan et al (US 2002/0192686 A1; 12/19/02).

Okabe et al teaches a method of defining the differentiation grade of a tumor with genes selected by statistical analysis comprising determining the number of genes to define the differentiation grade of tumor and using microarrays based on expression level or pattern of genes of human liver tumor tissues, wherein the differentiation grade of tumor is selected from the group consisting of non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC and wherein the genes are differentially expressed between non-cancerous liver and pre-cancerous liver, precancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC (see pages 2136-2137, in particular). Okabe et al further teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular).

Okabe et al does not specifically teach methods wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC. However, these deficiencies are made up in the teachings of Adorjan et al.

Adorjan et al teaches method of selecting cancer markers by using a Fisher ratio, referred to by Adorjan et al as a "Fisher criterion" (see paragraphs 0104-0105, in

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particular). Adorjan et al further teaches a Fisher ratio is a classical measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately identify particular tumor types because Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular) and Adorjan et al teaches a Fisher ratio is a “classical” measure to assess the degree of separation between two classes and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for determine the differentiation grade of a tumor with genes identified by Okabe et al by performing Fisher ratios with the expression data of Okabe et al wherein

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the genes that have the highest Fisher ratios are selected in descending order of a Fisher ratio wherein the Fisher ratios are from a comparison between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated HCC, well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC in order to accurately determine which markers of Okabe et al are associated with particular tumor types because Adorjan et al teaches how to perform a Fisher ratio and the Fisher ratio gives a high ranking for cancer markers where two classes are far apart compared to within class variations (see paragraphs 0104-0105, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al (Cancer Research, March 2001, 61: 2129-2137) in view of Adorjan et al (US 2002/0192686 A1; 12/19/02) as applied to claims 1-11 above, and further in view of Bloch et al (US 6,728,642 B2; 4/27/04).

The combined teaching of Okabe et al and Adorjan et al is discussed above.

The combined teaching of Okabe et al and Adorjan et al does not specifically teach a method wherein a minimum distance classifier with data of selected genes is designed and wherein a self-organizing map is generated with data of genes. However, these deficiencies are made up in the teachings of Boch et al.

Boch et al teaches a “minimum distance classifier” is a well-known cluster identification algorithm (see paragraph 0098, in particular). Boch et al further teaches illustrating classified genes into self-organizing maps (see Figures 10-11, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to design minimum distance classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a “minimum distance classifier” is a “well-known” cluster identification algorithm (see paragraph 0098, in particular), Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular), and Okabe et al teaches the importance of analyzing microarray data of tumor states using cluster analysis in order to see how genes are expressed and gain insight into cellular processes involved in various classes of tumor (see page 2137, in particular). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for designing minimum distance classifiers with the genes identified by the Okabe et al and Adorjan et al and generate a self-organizing map with data of the genes identified by the method of Okabe et al and Adorjan et al because Boch et al teaches a “minimum distance classifier” is a “well-known” cluster identification algorithm (see paragraph 0098, in particular) and Boch et al teaches organizing clusters for presentation by illustrating classified genes into self-organizing maps (see Figures 10-11, in particular). Therefore, the invention as a whole

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would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 40-46, 48-53, and 57-68 of U.S. Patent No. 11/484664. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 37, 40-46, 48-53, and 57-68 of U.S. Patent No. 11/484664 are species of instant claims 1-12.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Primary Examiner, Art Unit 1642